REMARKS

The First Claim Rejection Under 35 U.S.C. §§ 112, first paragraph

The Office Action alleges that the rejection of claim 16 remains because of the prior art discloses only partial sequences of CDRs from heavy and light chains for L19 and E1 and not the whole antibody of L19 and E1.

Applicants provided a reference by Pini et al., *Journal of Biological Chemistry*, vol. 273, pp. 21769-21776, 1998 (PUBMED ID: 9705314). The Office Action's contentions are misplaced. Although the E1 and L19 sequences were not explicitly recited in the aforementioned publication by Pini, these sequences could be routinely obtained without undue effort. Further, Pini states that these sequences were deposited in the EBI database. See, the legend to table II at page 21772 of Pini et al. A skilled worker could utilize routine search techniques for retrieving all the information relating to these sequence(s), for example, protein and/or nucleotide accession numbers. For example, the skilled worker could use CITEXPLORE, a program freely available from the European Bioinformatics Institute (EBI) website (http://www.ebi.ac.uk/citexplore/) to retrieve sequences (and accession numbers) which correspond to Pini et al.

A search in CITEXPLORE using PUBMED ID: 9705314 (Pini et al., 1998) dispenses the following protein/mRNA accession numbers and their respective sequences:

S/N	UNIPROT ID (protein)	EMBL ID (mRNA)	DESCRIPTION
1	**A2KBB9**	**AJ006111**	**Homo sapiens mRNA for E1 anti-(ED-B) scFV recombinant antibody, partial**
2	A2KBC0	AJ006112	Homo sapiens mRNA for H10 anti-(ED-B) scFV recombinant antibody, partial
3	**A2KBC1**	**AJ006113**	**Homo sapiens mRNA for L19 anti-(ED-B) scFV recombinant antibody, partial**
4	A2KBC2	AJ006114	Homo sapiens mRNA for A2 anti-(ED-B) scFV recombinant antibody, partial
5	A2KBC3	AJ006115	Homo sapiens mRNA for G4 anti-(ED-B) scFV recombinant antibody, partial
6	A2KBC4	AJ006116	Homo sapiens mRNA for H7 anti-TN-C scFv recombinant antibody, partial
7	A2KBC5	AJ006117	Homo sapiens mRNA for 17 anti-HCS scFv recombinant antibody, partial
8	A2KBC6	AJ006118	Homo sapiens mRNA for H1 anti-FactorVIII scFv recombinant antibody, partial
9	A2KBC7	AJ006119	Homo sapiens mRNA for A4 anti-IFN-G scFv recombinant

			antibody, partial
10	A2KBC8	AJ006120	Homo sapiens mRNA for C3 anti-TeTox scFv recombinant antibody, partial

Based on the description of the sequences/accession numbers, a skilled artisan can readily determine that the nucleotide with the accession number AJ006113 [GenBank Identifier (GI) No.: 3395509] relates to L19 sequence. Similarly, the nucleotide with the accession number AJ006111 [GenBank Identifier (GI) No.: 31523557] relates to the E1 sequence. The antigen-binding regions in the aforementioned antibody molecules could also be routinely determined based on Pini's own disclosure and/or utilizing programs such as BLAST and INTERPROscan. See, for example, Pini's experimental section and the disclosure contained in Fig. 1.

Furthermore, AJ006113 and AJ006111 comprise the most up-to-date version of the sequence which was deposited on the EBI database as of the priority date of the present application (based on the history of these deposits).

As such, the claimed antibody molecules were available to the skilled worker prior to the filing date of the instant application.

The Office Action alleged that the definition of Y being $=C(CH_3)_2$, is only supported for the single embodiment of example 1.

Applicants clearly provide a generic formula with a Y group therein with all other groups being as defined for the generic formula. Inadvertently, no definition for Y is provided for the general formula. However, a specific embodiment demonstrates that Y can be $=C(CH_3)_2$. Nothing in the application even remotely limits the definition of Y being $=C(CH_3)_2$ only in the context of example 1, and one of ordinary skill in the art would not understand such a limitation to be placed on the disclosure. Clearly there is an obvious error in the application by not having Y defined for the general formula. However, it is likewise clear to one of ordinary skill in the art that the definition of Y provided in example 1 is not limited to only the specific embodiment of example 1. Thus, one of ordinary skill in the art based on the disclosure would have readily understood that the definition of Y in example 1 is applicable to the definition of Y in the general formula. As such, the rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

The claims are rejected as allegedly obvious over Neri (Nature Biotechnology), in view of Viti, applicants' alleged admission in the specification, and Licha '485.

The Office Action finds the data inadequate for testing four conjugates while more is claimed. No other reason is provided. However, there is nothing wrong with claiming more than what is tested as long as the compounds tested are commensurate in scope with the claims. The four conjugates tested are representative of the claimed genus, i.e., commensurate in scope with the claims, and establish significant and unexpected results for the entire claimed genus over the cited prior art.

The law does not require an applicant to test each and every species of a claimed invention. For example, the Board's position in *Ex parte Winters*, 11 USPQ2d 1387 (BPAI 1989) is clearly stated on this issue in the following passage wherein the Board stated that

> appellant is **not required to test each and every species** within the scope of the appealed claims and compare same with the closest prior art species. Rather, patentability is established by a showing of unexpected superiority for ***representative*** compounds within the scope of the appealed claims. What is representative is a factual question which is decided on a case-by-case basis. (emphasis added)

In *Winters*, the Board faced a situation where the subgenus of compounds defined in the claim at issue embraced four species or a physiologically acceptable salt of those species, but the evidence presented in a declaration establishes that only one of the claimed species possessed unexpectedly superior results compared with the closest prior art compound. The board concluded that the declaration showing is adequately representative and rebuts the *prima facie* case of obviousness. The data provided in the present case is adequately representative of the invention claimed, and as long as the data is representative, such data must be taken as adequate for the demonstration of unexpected results.

The CCPA also addressed the adequacy of data in *In re Saunders*, 170 USPQ 213 (CCPA 1971). The CCPA stated, where an applicant provided a comparison for "only two" of the claimed species (surfactants) with the prior art species having the same molecular weight, that

> while appellants certainly did not isolate every possible variable and demonstrate that substitution of their surfactants invariably led to a superior result, we think their showing was adequate ... absent any reason to expect a different result with some other set of variables. (emphasis added)

Likewise in the present case, even though data on all species is not provided, there is no showing or rationale provided by the Office Action by which one would expect a different result if the antibody-dye conjugate was changed to another suitable antibody-dye conjugate of the claims.

In re Cescon, 177 USPQ 264 (CCPA 1973), is another relevant case. In *Cescon* the claimed composition was known to exhibit the phenomenon of phototropism, i.e., their change in color upon exposure to light and reversal upon removal of the stimulus (the phototropism itself thus not unexpected), the applicants discovered that the presence of an ortho substituent in the 2-phenyl ring imparted an improved responsiveness to changes in light intensity. The prior art disclosed several precursor compounds in the same class (imidazolyl radicals) having ortho substitutions, including teachings on how to make the claimed compounds, but did not teach the desirability to make them over other imidazolyl compounds. The prior art did not teach or suggest any relationship between ortho substitutions and the 2-phenyl ring and the properties discovered by applicants. The court held the data sufficient to overcome the rejections even though the examples were limited to a benzene solution. The court stated:

> Our disagreement with the action of the Patent Office at this level arises from **overly stringent standards set up for evaluating appellant's objective evidence**. It is true that the claims are broadly drawn to the presence of the imidazolyls in the environment of an inert solvent or substrate. The **examples** providing comparisons with analogously substituted isomers or unsubstituted imidazoles, on the other hand, are **limited to the use of a benzene solution**. Not all compounds encompassed by the claims are tested. But ample data has been provided to establish the correlation between ortho substitution on the 2-phenyl ring and greatly increased color fading rates. Moreover, no factual basis appears in the record for expecting the compounds to behave differently in other environments. (emphasis added)

Also see *In re Kollman*, 201 USPQ 193 (CCPA 1979) holding that

> we feel that **the unobviousness of a broader claimed range can ... be proven by a narrower range of data**. Often, one having ordinary skill in the art may be able to ascertain a **trend** in the exemplified data which would allow him to reasonably **extend the probative value thereof**. The proof, thus considered, might then be sufficient to rebut a PTO holding of prima facie obviousness. (emphasis added)

In the present case the amount of data submitted clearly establishes to one of ordinary skill in the art that the antibody-dye conjugates according to the claimed invention provide a significantly better immunoreactivity, which in practice leads to better tumor imaging efficacy, over the comjugate of Neri et al. One of ordinary skill in the art can easily extend the probative value of the data on the four antibody-dye conjugates to the rest of the claimed genus.

The courts consistently held that not all species of a claimed invention need to be tested in order to demonstrate unexpected results. Applicants provided representative examples which establish that the claimed invention has unexpected properties. No reason or rationale is provided which would establish that a different catalyst than tested in the claimed invention would behave differently. Therefore, the unexpected results demonstrated should be adequate to establish the patentability of the claimed invention.

Additionally, a mere allegation that the other species of the invention are expected to behave differently or would behave differently under different conditions than the specific ones exemplified would not be adequate to rebut a showing of unexpected results. The Board in *Winters*, supra, gave no weight to the "the examiner's speculation that the declaration evidence may reflect only an anomalous 'interaction' between the 2-methylpropyl group and the 2-methylphenyl group which causes an unexpected and surprising increase in potency for the claimed species ... [because the speculation was] not supported by any facts of record or by sound scientific reasoning." Thus, the grounds for finding data inadequate and/or not representative, i.e., not commensurate in scope with the claimed invention, should be based on facts of record or on sound scientific reasoning. No such facts of record and/or sound scientific reasoning have been put forth by the Patent Office.

The Examiner also alleges that a direct comparison should be done in the same system as in the references. However, this is not the case under the law. No case has held that the tests must be done in the context of the prior art invention. Also, the Office Action provides no reason or rationale, e.g., nothing scientifically based as to why tests conducted within the same system as in the references would be more probative of whether the claimed compounds demonstrate significant and unexpected advantages over the prior art. It is probably true that some differences in performance from one system to the next may be observed, but a parameter that would affect one conjugate in a specific manner would probably affect a different conjugate in a similar manner, even if arguably to a slightly different level or extent. Without any rationale provided as to why the prior art system is necessary, applicants submit

that the Office Action has not provided a legitimate reason under the law for requiring further data or data in a different system.

The Office Action also alleges that the *in vitro* data used does not correlate to the *in vivo* data despite the data demonstrating better immunoreactivity. This is a bare allegation. Again, no scientific rationale or explanation is provided as to why the *in vitro* data used does not correlate to the *in vivo* data. Instead, generally, unless there is a reason based in fact to doubt the correlation, the courts have specifically held contrary to the position of the Office Action. The Federal Circuit in *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), stated that

> in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Moreover, the declaration states that the data demonstrating better immunoreactivity "in practice lead to better tumor imaging efficacy." The Office Action again has no basis for substituting its own conclusions or opinion in place of the conclusions of the expert signing the declaration. As clearly stated in *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963):

> If that which appears, at first blush, to be obvious though new is shown by evidence *not* to be obvious then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall. (Emphasis added.)

Reconsideration is respectfully requested.

Double Patenting Rejections

A terminal disclaimer was filed rendering the rejection moot. Yet the Office Action alleges that "while filing a terminal disclaimer, applicant did not address the issue of common ownership." Applicants confirm that the reference over which this application is disclaimed is co-owned by the same entity as the current application.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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